

General comment- This is a clearly presented and well-written paper from Dr. Chengmu Hu's group. In this manuscript, the authors examined the role of caveolin-1 in alleviating APAP-induced hepatotoxicity in alcoholic fatty liver disease (AFLD) by regulating the angiotensin II/EGFR/ERK pathways. AFLD affects the people worldwide. Its manifestations ranges from steatosis, NASH, cirrhosis to HCC. Currently, there is no drug for AFLD therapy. Overuse of over the counter drug acetaminophen (APAP, common analgesic) may lead to hepatocyte necrosis and liver failure. The following study demonstrate the mechanistic role of caveolin-1 in alleviating APAP-induced hepatotoxicity in AFLD by regulating the angiotensin II/EGFR/ERK axis.

Summary of the salient findings:

Using AFLD mice model and in vitro L02 cells, authors demonstrated the protective effect of caveolin-1 on APAP-induced hepatotoxicity. Overexpression of CAV1 alleviating hepatotoxicity and downregulated Ang II, p-EGFR/EGFR and p-ERK/ERK expression. Also, application of Ang II receptor, ERK1/2 antagonists alleviated APAP induced hepatotoxicity in AFLD.

The proposed study is very interesting, results are explained well but I have the following comments and concerns.

1. Caveolin-1 protein expression reduced in AFLD models (role in the pathogenesis of AFLD). However it's not how caveolin 1 expression is regulated. Does it also affects caveolin-1 mRNA level ?
2. Caveolin-1 alleviates APAP induced hepatotoxicity in AFLD. There is no mention about the clinical relevance. What is the status of caveolin-1 expression in clinical settings?
3. Authors demonstrated blocking of autophagy and restoration of autophagic flux with Caveolin overexpression.

In Fig4 B, LC3II protein level & densitometry is not matching with Fig. 6E. From Fig4b WB there looks an increase in LC3II to LC3I expression in LV-ctrl + Etoh +APAP condition but densitometric analysis shows reduction which is not in line with fig6E where graph show increase in similar settings (LV-ctrl + Etoh +APAP).

4. Minor comments-

a) In line 7, there is extra space between Institute of and Innovative.

I recommend the manuscript be accepted for publication, with addressing these concerns